ASTRAZENECA AB *WO 2003068754-A1

2002.10.22 2002-003122(+2002SE-000450) *(2003.08.21)* C07D 231/56, A61K 31/341, 31/4025, 31/416, 31/4427, C07D 403/04, 405/04, 401/12, A61P 9/00, 25/00, 35/00

New indazole derivatives are c-Jun terminal kinase inhibitors used for treating e.g. Alzheimer's disease and cognitive disorders and Parkinson's disease (Eng)

C2003-189122 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW) R(AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW)

Addnl. Data: MALMSTROEM J, SWAHN B

2003.02.11 2003WO-SE00227, 2002.10.22 2002SE-003122.

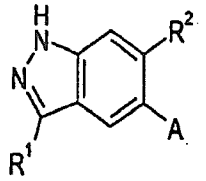
B(6-D5, 14-C1, 14-C3, 14-C4, 14-C9, 14-D6, 14-G1B, 14-H1, 14-J1A3, 14-J1A4, 14-N16) .7

NOVELTY

Indazole derivatives (I) are new.

DETAILED DESCRIPTION

Indazole derivatives of formula (I) and their salts are new.



(I)

R^1 = aryl or heteroaryl (both optionally substituted by at least one R^3, OR^3, $OCOR^3$, $COOR^3$, COR^3, $CONR^3R^4$, $NHCOR^3$, NR^3R^4, $NHSO_2R^3$, SO_2R^3, $SO_2NR^3R^4$, SR^3, CN, halo or NO_2);

R^2 = NO_2, NH_2, NR^5R^6 or NR^6R^7;

R^3, R^4 = 1-6C alkyl, 2-6C alkenyl, 3-8C cycloalkyl-(0-6C)alkyl, 1-6C fluoroalkyl, heterocycle-(0-6C)alkyl or heteroaryl-(0-6C)alkyl (all optionally substituted by at least one B') or H, or

WO 2003068754-A+

$R^3 + R^4$ = 5-7 membered heterocyclyl containing 1-4 N, O or S heteroatoms (optionally substituted by at least one B');

B' = T, COR^{10} or oxo;

T = R^{10}, $COOR^{10}$, $NHCOR^{10}$, $NR^{10}R^{11}$, $CONR^{10}R^{11}$, OR^{10}, $SO_2NR^{10}R^{11}$, CN or halo;

R^5 = phenyl or heteroaryl (both optionally substituted by at least one T, $OCOR^{10}$, $NHSO_2R^{10}$, SO_2R^{10}, SR^{10} or NO_2);

R^6 = H, 1-6C alkyl, heterocycle(0-6C)alkyl or hydroxy(1-6C)alkyl;

R^7 = 1-6C alkyl, 3-8C cycloalkyl(0-6C)alkyl, 5-8C cycloalkenyl(0-6C)alkyl or R^5(1-6C)alkyl;

A = H, R^8, OR^8, $OCOR^8$, $COOR^8$, $CONR^8R^9$, $NHCOR^8$, NR^8R^9, $NHSO_2R^8$, SO_2R^8, $SO_2NR^8R^9$, SR^8, CN, halo, heterocycle(0-6C)alkyl or heteroaryl(0-6C)alkyl;

R^8, R^9 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, heterocycle(0-6C)alkyl or heteroaryl(0-6C)alkyl (all optionally substituted by at least one B'), or H, or

$R^8 + R^9$ = 5-7 membered heterocyclyl containing 1-4 N, O or S heteroatoms (optionally substituted by at least one B'), and

R^{10}, R^{11} = H, 1-6C alkyl, 1-6C fluoroalkyl or hydroxy(1-6C)alkyl, or

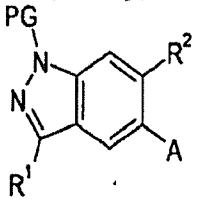
$R^{10} + R^{11}$ = 5-7 membered heterocyclyl containing 1-4 N, O, or S heteroatoms (optionally substituted by at least one B'),

provided that (I) is not 6-amino-3-(4-fluorophenyl)-indazole, 6-amino-3-phenyl-indazole, 6-nitro-3-phenyl-indazole and 6-nitro-3-(4-nitrophenyl)-indazole, and has no quinazoline in the R^5 position.

INDEPENDENT CLAIMS are also included for:

(1) new intermediate compounds of formula (II), and

(2) preparation of (I) by deprotecting (II).



(II)

R5 -X = reactant

PG = amino protecting group.

ACTIVITY

Neuroprotective; Nootropic; Antiparkinsonian; Anticonvulsant; Anti-HIV; Cytostatic; Antiinflammatory; Antipyretic; Analgesic.

MECHANISM OF ACTION

c-Jun N-terminal kinase (JNK) inhibitor.

WO 2003068754-A+/

2003-689639/65

In a scintillation proximity assay (SPA) based on the inhibition of JNK3 catalyzed transfer of the γ-phosphate group of [γ^{33}P] adenosine triphosphate (ATP) to biotinylated activating transcription factor (ATF)-2, (I) exhibited K_i values of 0.001-10000 (especially 0.001-300) nM.

USE

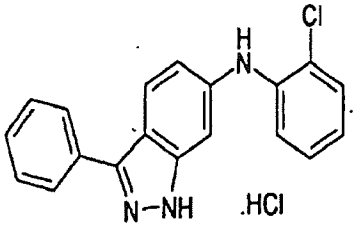
Used central or peripheral neurological degenerative disorders including Alzheimer's disease, cognitive disorders, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia Parkinson's type, Parkinson dementia complex of Gaum, HIV dementia, corticobasal degeneration, dementia pugilistica, Down's syndrome, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's disease, Niemann-Pick's disease, epilepsy, peripheral neuropathy, spinal cord injury, head trauma, cancer, edema, analgesia, fever and pain (e.g. neuromuscular pain, headache, cancer pain, dental pain and arthritis pain) (all claimed).

ADVANTAGE

(I) Are potent inhibitors of JNK, which inhibit the expression of inducible proinflammatory proteins.

SPECIFIC COMPOUNDS

64 Compounds (I) are specifically claimed e.g: (2-chlorophenyl)-(3-phenyl-1H-indazol-6-yl)-amine hydrochloride (Ia).



(Ia)

ADMINISTRATION

The dosage is 0.01-250 mg/kg/day perorally or 0.001-250 mg/kg/day parenterally.

WO 2003068754-A+/

(con't)

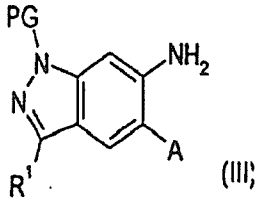
EXAMPLE

Palladium acetate (15.1 mg) and (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((S)-BINAP) (61.2 mg) were mixed in dry tetrahydrofuran (3 ml) for 5 minutes under a nitrogen atmosphere. 1-Bromo-2-chlorobenzene (75 µl) and 6-amino-3-phenyl-indazole-1-carboxylic acid tert-butyl ester (199.8 mg) were added, followed by cesium carbonate (295.5 mg). The reaction was stirred at 60°C for 7 hours under a nitrogen atmosphere. Then, additional palladium acetate (15 mg), ((S)-BINAP) (61.4 mg) and 1-bromo-2-chlorobenzene (75 µl) were added. The reaction mixture was stirred at 60°C for 18 hours, followed by work-up to give 6-(2-chloro-phenylamino)-3-phenyl-indazole-1-carboxylic acid tert-butyl ester.

To a solution of this compound (144.3 mg) in methanol (2 ml) was added 4M HCl in diethylether (1 ml). The reaction mixture was stirred at ambient temperature for 24 hours. The solvent was evaporated and work up produced (2-chlorophenyl)-(3-phenyl-1H-indazol-6-yl)-amine hydrochloride (Ia) (117.1 mg; 87%).

TECHNOLOGY FOCUS

Organic Chemistry - Preparation (claimed): Preparation of (I) comprises e.g. reacting an amine compound of formula (III) with R^5-X and deprotecting (II: $R^4 = NR^7R^8$; $R^8 = H$) to give (I: $R^2 = NR^5R^6$; $R^6 = H$).



(III);

(35pp8032DwgNo.0/0)